UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/500,162	02/08/2000	Judes Poirier	08523/006002	2201

21559 7590 08/13/2003

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER
PARKIN, JEFFREY S

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 08/13/2003

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/500,162	POIRIER, JUDES	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-8,10-14 and 17-20* is/are pending in the application.

4a) Of the above claim(s) *17-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-8 and 10-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Response to Amendment

Status of the Claims

1. Acknowledgement is hereby made of receipt and entry of the amendment filed 05 May, 2003, wherein claims 4, 9, and 15 were canceled without prejudice or disclaimer and claims 1, 5, 6, 10, 11, and 12 amended. Claims 1, 3, 5-8, 10-14, and 17-20 are pending in the instant application. This application contains claims 17-20 drawn to an invention non-elected with traverse. A complete response to the final rejection must include cancellation of non-elected claims or other appropriate action (refer to 37 C.F.R. § 1.144 and M.P.E.P. § 821.01). Claims 1, 3, 5-8, and 10-14 are currently under examination.

Information Disclosure Statement

2. The information disclosure statement filed 05 May, 2003, has been placed in the application file and the information referred to therein has been considered.

35 U.S.C. § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

4. The previous rejection of claims 1, 3, 4, and 12 under 35 U.S.C. § 102(a) as being clearly anticipated by Roberts *et al.* (1996), is hereby withdrawn in response to applicant's amendment.

35 U.S.C. § 103(a)

5. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

6. The previous rejection of claim 11 is under 35 U.S.C. § 103(a) as being unpatentable over Roberts *et al.* (1996), is hereby withdrawn in response to applicant's amendment.

7. The previous rejection of claims 1, 3, 4, 11, 12, and 15 under 35 U.S.C. § 103(a) as being unpatentable over Morris *et al.* (1996) in view of Poirier *et al.* (1995), is hereby withdrawn in response to applicant's declaration.

35 U.S.C. § 112, First Paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 3, 5-8, and 10-14 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

commensurate in scope with these claims. As previously set forth the claimed invention is broadly directed toward the use of *apo*E allele determinations to predict the clinical efficacy of a given drug in patients with various neuropathologies. The disclosure describes a method for creating a prognostic protocol for late onset Alzheimer's disease (AD) patients by examining ApoE protein levels. It was reported that individuals carrying one or both copies of the ε4 allele display a poorer clinical outcome as compared to those late onset AD patients lacking the allele. Thus, the claimed invention is enabled only as it applies to late onset AD patients. Applicants were advised that appropriately drafted claim language directed toward this embodiment would be acceptable. However, the disclosure is not enabling for claim language directed toward any and all other neurological diseases.

The legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The amended claims are still excessively broad and encompass an extremely large genus of disparate neurological disorders. The specification defines neurological diseases (see p. 7) to include the following: Alzheimer's Disease (AD), prion diseases (e.g., Creutzfeldt-Jakob disease), pathologies of the developing brain such

as congenital defects in amino acid metabolism (e.g., arginosuccinic aciduria, cystathionuria, histidinaemia, homocystinuria, hyperammonaemia, phenylketonuria, fragile X syndrome), neurofibromatosis, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, stroke, brain injuries due to trauma, and other various pathologies. **These sundry disorders all have different pathological determinants (Martin and Longo, 1998; Timchenko *et al.*, 1996; Salvatore *et al.*, 1995; Brouillet *et al.*, 1995). The molecular determinants modulating many of these disorders have been mapped to chromosomal regions unrelated to those of late onset Alzheimer's disease (see Table 363-1, pp. 2294-2303). Moreover, for those neurological disorders with a clear mechanism of disease, most of them do not involve the Apolipoprotein E4.** For instance, Creutzfeldt-Jakob disease is caused by a prion protein, Wilson's disease is caused by a defective membrane ATP-ase, amyotrophic lateral sclerosis is caused by a mutant superoxide dismutase (*SOD*1), other forms of amyotrophic lateral sclerosis have been attributed to a mutant neurofilament heavy chain protein, and fragile X syndrome is caused by trinucleotide repeats in the 5′ region of the *FMR*-1 gene. Thus, **many of these disorders fail to share any genetic linkages or biochemical mechanisms with those of late onset AD and *apo*E allele frequency.** Accordingly, **the skilled artisan would not consider it reasonable to assert that the *apo*E allele frequency in all these various disorders, many of which do not directly involve Apo E-regulated transport and internalization of cholesterol and phospholipids, would be predictive of therapeutic responsiveness and clinical outcome.** Furthermore, even if the underlying mechanism did affect lipid metabolism, it does not mean that changes in the *apo*E allele load are responsible for the defect. The defect could be present in a downstream or upstream step of the pathway independent of the presence or absence of any given *apo* E

allele. The disclosure clearly fails to provide sufficient guidance pertaining to this concern.

2) The disclosure fails to establish any correlation between *apo*E ε4 allele loads and any given neurological disorder other than AD. As noted in point (1) *supra*, the molecular basis for many non-AD neurological disorders remains to be elucidated. For those disorders that have been characterized, most of them do not involve disorders of ApoE-regulated transport and internalization of cholesterol and phospholipids (Martin and Longo, 1998). Thus, the disclosure fails to provide any guidance pertaining to the specificity, sensitivity, and predictive value of measuring the *apo* E allele frequency in any of these disorders.

3) The disclosure fails to provide adequate guidance pertaining to the predictive value of measuring *apo*E allele loads with any particular class of therapeutics. In AD, the *apo*E ε4 allele load is reasonably predictive of patient responsiveness to cholinomimetic therapy. This is not surprising considering the finding that late-onset AD patients have decreased levels of choline and decreased ChAT activity. However, the disclosure fails to provide any guidance pertaining to other suitable therapeutic compounds and the predictive value of measuring the *apo*E allele load in these settings.

4) The disclosure fails to provide any working embodiments involving non-AD neurological disorders. The only example provided involves the relationship between *apo*E allele frequency and cholinomimetic responsiveness in late-onset AD patients. Examples involving non-AD neurological disorders were not provided.

5) The prior art clearly teaches that *apo* E allele frequencies do not correlate with most non-AD neurological disorders. For example, Morris *et al.* (1996) state(abstract, p. 205) that "We have genotyped a large series of clinically and neuropathologically confirmed cases of AD ... **No changes in APO E allele frequencies were found in**

presenile AD, Parkinson's disease with or without dementia, or in Down's syndrome." The authors further reported (abstract, p.205) that "Whilst there appears to be a strong association between the APO E allele and AD and also in LBD, **other related neurodegenerative disorders associated with dementia do not show such a linkage."** The authors were unable to demonstrate any apparent association between APO E ε4 levels and vascular dementia, Parkinson's disease, alcoholic dementia, and Down's syndrome (p. 207, bottom paragraph). The authors further summarized their studies and reported (p. 212, first full paragraph) that **"Recent studies (Saunders et al., 1993; Pickering-Brown et al., 994; Royston et al., 1994; Martins et al., 1995; Wisniewski et al., 1995) have failed to show an increased ε4 frequency in Down's syndrome patients, and the present results would appear to confirm this"** and that (p. 212, second paragraph) **"Both demented and non-demented Parkinisonian patients showed no significant increase in APO E ε4 frequence, compared to age-matched controls, suggesting that the biological basis of dementia in PD differs from that found in AD and LBD and is not linked to APO E (Benjamin et al., 1994; Koller et al., 1995; Marder et al., 1994)."** Additional studies by Mattila *et al.* (1998) confirmed these findings. The authors reported (abstract, p. 417) that **"The results show that neuropathologically verified PD as such is not associated with increased apoε4 allele frequency."** It was further noted (p. 419, first paragraph, Discussion) that "our results confirm the findings of clinical series [3, 11, 14] showing no increase in **apoε4** allele frequency in PD. The results of most of the previous neuropathological series of PD [4, 9, 26] were also similar to those in our study." Earlier work by Rubinsztein *et al.* (1994) was also consistent with these findings. The authors noted (p. 519, abstract and p.523, rt. col.) that **"No significant alteration in the apo E allele distributions was observed in any of these conditions [i.e.,**

multiple sclerosis, Parkinson's diseases, sporadic vestibular schwannomas, and neurofibromatosis], nor did the apo E genotypes correlate with disease severity" and "No significant associations were detected with any of the apo E alleles or genotypes with multiple sclerosis or Parkinson's disease. In addition, no relationship was detected between the onset of Parkinson's disease and any apo E genotype. It is thus unlikely that apo E plays an important role in the pathogenesis of these diseases." Salvatore *et al.* (1995) also reported (refer to Abstract, page 95) that "Our results provide further evidence that ApoE is not a risk factor for CJD." Finally, Marder *et al.* (1994) also observed (p. 1330, abstract) that "There was no association between Apoε4 and dementia in the PD patients. We conclude that the biologic basis for dementia in PD may differ from that of AD." Thus, the prior art clearly illustrates that the *apo*E ε4 allele is not responsible for many neurological deficits. Therefore, determining the *apo*E allele load would be of no predictive value.

Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention in a manner commensurate in scope with the claims.

Response to Arguments

10. First, applicant asserts that post-filing date references validate the claimed methodology (Fazekas *et al.*, 2000; Drory *et al.*, 2001; Leung *et al.*, 2002). Applicant is reminded that in order to overcome a *prima facie* case for lack of enablement, applicant must demonstrate that the disclosure was enabled as of the filing of the application (see M.P.E.P. § 2164.05(a)). Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at

the time of filing. *In re Gunn*, 537 F.wd 1123, 1128, 190 U.S.P.Q. 402, 405-06 (C.C.P.A. 1976). *In re Budnick*, 537 F.2d 535, 538, 190 U.S.P.Q. 422, 424 (C.C.P.A. 1976). The publications relied upon were all published well after the effective filing date of the instant application. Moreover, assuming arguendo that the references relied upon were reflective of the state-of-the-art, they still fail to address many of the deficiencies set forth *supra*. Thus, at best, the claims might be enabled for the particular species recited in those particular publications. However, these publications would still fail to provide adequate support for the breadth of the claimed invention.

Second, applicant argues that the references relied upon by the Examiner are not germane to the claimed invention. This assertion is clearly erroneous. The claims are directed toward a prognostic protocol that involves determining the *apoε*4 allele load in a patient with any one of a number of unrelated nervous system disorders. The presence of the E4 allele has been associated with a poor clinical outcome in a single neurological disorder (e.g., Alzheimer's disease [AD]). In order to enable the breadth of the claimed invention, which is directed toward a number of sundry and unrelated neurological disorders, the disclosure would need to provide a nexus between the *apoε*4 allele load and these various pathologies. The references relied upon clearly demonstrate that the ApoE4 protein does not play a role in a number of the pathologies currently covered by the claims. Accordingly, the skilled artisan would reasonably question the usefulness of measuring *apoε*4 allele loads in these disparate neurological disorders to assess or predict the clinical outcome.

Third, a declaration was provided by the inventor, Dr. Judes Poirier, which discusses the three post-filing date references relied upon. This issue has already been dealt with in the preceding paragraphs. The declarant also referenced three other studies (raw

data and experimental methodologies were not provided) wherein it was asserted that there was a negative clinical outcome associated with the presence of the *apoε*4 allele. Interestingly, in one of the studies directed toward stroke patients the inventor stated that "I did **not** observe a negative outcome in stroke patients that carried the *apoE*4 allele using these parameters." It was asserted that the other two studies (involving PD and MS patients) illustrated that the presence of the *apoε*4 allele was correlated with a decreased positive clinical outcome. Applicant is reminded that the claims encompass an exceedingly large genus of unrelated neurological disorders. The assertion that two species of this genus may share a common mechanistic pathway is still insufficient to support the full breadth of the claimed invention as set forth supra. The declaration and disclosure fail to provide a common biochemical nexus between the sundry neurological disorders covered by the claim language.

Non-statutory Double Patenting

11. The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 U.S.P.Q. 644 (C.C.P.A. 1969); *In re Vogel,* 422 F.2d 438, 164 U.S.P.Q. 619 (C.C.P.A. 1970); *In re Van Ornum,* 686 F.2d 937, 214 U.S.P.Q. 761 (C.C.P.A. 1982); *In re Longi,* 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985); and *In re Goodman,* 29 U.S.P.Q.2d 2010 (Fed. Cir. 1993). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d). Effective January 1, 1994, a

registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. § 3.73(b).

12. Claims 1, 3, 5-8, and 10-14 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,935,781. Although the conflicting claims are not identical, they are not patentably distinct from each other. Applicant's argument that the claims of the instant application are directed toward and independent and distinct invention are not persuasive. As previously set forth, the claims of the instant application are directed toward prognostic protocol methods involving patients with neurological disorders and *apo*E allele load determinations while the claims of the '781 patent are directed toward patient prognostic protocols involving patients with cognitive impairments, which are caused by CNS pathologies. Thus, the claims of the '781 patent fall within the scope of the claimed invention and would result in the unjustified or improper timewise extension of the "right to exclude" granted by a patent.

13. Claims 1, 3, 5-8, and 10-14 stand **provisionally** rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 09/865,753. Although the conflicting claims are not identical, they are not patentably distinct from each other. As previously set forth, the claims of the instant application are directed toward prognostic protocol methods involving patients with neurological disorders while the claims of the '753 application are directed toward prognostic protocol methods involving patients with a non-AD neurological disorder. Thus, the claims of the '753 application anticipate the claims of the instant application and would result in the unjustified or improper timewise extension of the "right to

exclude" granted by a patent. This is a **provisional** obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Applicant has indicated that a terminal disclaimer will be filed upon the identification of allowable subject matter.

Finality of Office Action

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). **A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.**

Correspondence

15. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242 or (703) 305-3014. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

16. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 8:30 AM to 6:00 PM. A message may be left on the examiner's voice

mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, James Housel or Laurie Scheiner, can be reached at (703) 308-4027 or (703) 308-1122, respectively. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

08 August, 2003

LAURIE SCHEINER
PRIMARY EXAMINER